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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 July 2001 (12.07.2001)

PCT

(10) International Publication Number
WO 01/49269 A1

(51) International Patent Classification[7]: A61K 9/22

(21) International Application Number: PCT/KR00/01535

(22) International Filing Date:
26 December 2000 (26.12.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1999/65917 30 December 1999 (30.12.1999) KR

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/49269 A1

(54) Title: SUSTAINED-RELEASING ANTHELMINTIC COMPOSITIONS COMPRISING PRAZIQUANTEL

(57) Abstract: The present invention relates to a sustained-releasing anthelmintic composition, which contains praziquantel as an active ingredient and provides a controlled releasing rate of praziqantel by adequate selection and combination of a polymeric material and a binder.

SUSTAINED-RELEASING ANTHELMINTIC COMPOSITIONS COMPRISING PRAZIQUANTEL

TECHNICAL FIELD

The present invention relates to a sustained-releasing anthelmintic composition, which contains praziquantel as an active ingredient and provides a controlled releasing rate of praziqantel by adequate selection and combination of a polymeric material and a binder.

BACKGROUND ART

In present, it has been reported that trematode infections such as clonorchiasis, schistosomiasis, paragonimiasis, etc., and various taenia infections exhibit a very high positive rate for eggs mainly in developing countries and backward countries and several hundred millions of persons have suffered from such infections in the world. Particularly, infection with *Clonorchis sinensis* leads to cholangitis, suppurative cholangitis, cholelithiasis, cholangioma, cholangic liver cirrhosis, etc., thereby causing serious problems in clinical field, and further, thus greatly increases the burden of social expenses. Therefore, the treatment of such infections as clonorchiasis, etc., is a medical and social subject, which requires to be urgently solved.

Praziquantel as the active ingredient used in the present invention is a known drug, which was first developed as an agent for treatment of such trematode infections as schistosomiasis, clonorchiasis, paragonimiasis, etc., and various taenia infections by Bayer AG, Germany in the later half of 1970's and have been widely used in the world.

For treatment of clonorchiasis, praziquantel is administered three times in an amount of 25 mg/kg at intervals not more than 5 hours. The drug administered via

oral route is immediately absorbed in the upper part of small intestine to provide the maximum blood concentration 4 hours after administration, after which the blood concentration rapidly decreases. Although most of praziquantel in blood is excreted via urine, some extent thereof may be excreted via bile juice with metabolizing during it passes through liver. Since *Clonorchis sinensis* is parasitic on bile duct and therefore, can be destroyed by the drug excreted into bile duct, the concentration of praziquantel excreted into the bile duct has an important meaning. It has been disclosed that praziquantel excreted into bile duct is present in an amount smaller than its blood concentration, and further, is in an already metabolized form, and therefore, exhibits an anthelmintic effect reduced to 1/100 and less in comparison to the effect of praziquantel in blood. Thus, it is practically important that an effective anthelmintic concentration of praziquantel in bile juice should be maintained for 10 hours or more. The method for administration of praziquantel as mentioned above is a method, which can maximize the anthelmintic effect of praziquantel in bile juice by maintaining its blood concentration at the level of 1 μg/ml or more, which provides the standard of dosing this drug.

Further, in order to combat *Distoma haematobium* parasitic mainly on blood vessel, praziquantel is administered two times in a dose of 30 mg/kg at intervals of 5 hours. In case of paragonimiasis, praziquantel is administered for 2 to 3 days in the same dose as in case of clonorchiasis, and cysticercosis can be treated by administration of praziquantel in the same dose for about 2 weeks. In case of trematodes and taenias which are parasitic on intestine, a single dose of 10 mg/kg provides a sufficient effect. Such differences in dose and usage are dependent on parasitic sites and on whether the drug acts either directly by itself or after it is metabolized.

However, in general, if any drug is administered over several times, it is difficult to keep the usage prescribed for self-treatment. For currently commercially

available praziquantel preparations, it is prescribed that it should be repeatedly administered at regular intervals, and therefore, many persons cannot keep the prescribed time for administration, which causes a decrease in the desired anthelmintic effect. Due to such problem related to a compliance with dosing praziquantel, in many cases it is very difficult to obtain the desired anthelmintic effect by self-treatment with praziquantel. Further, overdose of praziquantel may cause resistant worms and also may result in serious side effects (pyrexia, headache, vomiting, drowsiness, abdominal pain, diarrhea, eczema, etc.) depending on individual subject.

Therefore, in order to obtain the desired effect in treating clonorchiasis, etc. it is necessarily required to develop an effective preparation, which can maintain the desired effect even by a single dose.

DISCLOSURE OF THE INVENTION

The present inventors supposed that if praziquantel can be controlled so as to be slowly absorbed within intestine, its dosage itself can be reduced, its administration is convenient due to its simple usage, its therapeutic effect against various trematodes and taenias infections in tissues can be greatly improved, and further the occurrence of resistant worms and side effects can be prevented, and thus, have studied to design a certain sustained-releasing preparation from which the releasing rate of praziquantel is controlled in a manner that praziquantel can be slowly absorbed within intestine . As a result, we have identified that a sustained releasing preparation according to the present invention, which is constituted by adequate selection and combination of a polymeric material and a binder, exhibits a sufficiently satisfactory result in a in vitro test for drug release, a test for anthelmintic effect in experimental animals and a test for

pharmacokinetic properties in the body, and thus, completed the present invention.

Therefore, the purpose of the present invention is to provide a composition for effectively combating various trematodes and taenias, from which praziquantel is released in a controlled manner.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention relates to a sustained-releasing anthelmintic composition, which contains praziquantel as an active ingredient and provides a controlled releasing rate of praziqantel by adequate selection and combination of a polymeric material and a binder.

More specifically, the present invention relates to a sustained-releasing anthelmintic composition which comprises praziquantel; a polymeric material selected from the group consisting of hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, methylcellulose and ethylcellulose; a filler selected from the froup consisting of alkyl alcohol, fatty acid and salts thereof; and a binder.

The polymeric material used in the present invention is a water-swelling polymeric material with hydroxypropyl cellulose and hydroxypropyl methylcellulose being particularly preferable. It is preferable that the polymeric material is contained in a ratio of 20 to 60 wt% with respect to a total weight of the composition.

As the filler which can be used in the present invention, stearic acid or stearyl alcohol is particularly preferable. The filler can be contained preferably in a ratio of up to 20 wt% with respect to a total weight of the composition.

Any conventional binder can be used as the binder in the present invention with polyvinyl pyrrolidone or hydroxypropyl cellulose having a low level of substitution

being particularly preferable. The binder can be contained preferably in a ratio of 1.5 to 8.5 wt% with respect to a total weight of the composition.

The composition of the present invention can be formulated into a pharmaceutical preparation such as tablet or capsule, which can be prepared according to any conventional method. The hardness of tablet is preferably 20 kg/cm^3 or more.

As a result of in vitro test for the composition of the present invention, it has been identified that the composition of the present invention slowly releases praziquantel as the active ingredient over at least 10 hours in comparison to the prior art praziquantel preparations (see Experiment 1). In addition, in vivo test it has also been confirmed that the composition of the present invention maintains the effective blood concentration of praziquantel to be 1 μg/ml for 12 hours or more in comparison to the prior art praziquantel preparations (see Experiment 2). Therefore, since the sustained-releasing preparation according to the present invention can continuously maintain the effective blood concentration of praziquantel even by a single administration, it can exhibit the substantially identical effect as continuous administration of the prior art preparations. According to the comparative experiment for anthelmintic effect of the composition of the present invention over the prior art preparation, it could be confirmed that even a single administration of the composition of the present invention can exhibit similar effect to three-times administration of the prior art preparations (see Experiment 3).

The anthelmintic preparation according to the present invention can be administered via oral route in a single dose of 10 to 150 mg/kg of body weight, preferably 30 to 100 mg/kg of body weight, to combat *Clonorchis sinensis, Distoma haematobium, Paragonimus westermani* and various taenias.

The present invention will be more specifically illustrated by the following examples. However, it should be understood that these examples are not to be

construed as limiting the scope of the present invention.

EXAMPLES

Example 1

(1) Mixing

The following components were introduced into a mixer in the given % by weight and then mixed together:

Praziquantel	48.4%
Hydroxypropyl methylcellulose	48.4%
Polyvinyl pyrrolidone	2.4%
Magnesium stearate	0.8%

(2) Preparation of tablets

The mixture obtained from the above (1) was compressed into a tablet by means of a rotary-type compressor so that the average hardness of tablet is 20 kg/cm^3 or more.

(3) Preparation of capsules

The mixture obtained from the above (1) was mixed with a mixed solution of water for granulation (30%) and ethanol (70%) and then granulated, and the resulting granules were dried over a plate drier. The granules thus prepared were passed through a 16 mesh screen to establish the granules having a uniform size, which were

then filled in No.1 type capsule.

Example 2

(1) Mixing

The following components were introduced into a mixer in the given % by weight and then mixed together:

Praziquantel	44%
Hydroxypropyl methylcellulose	44%
Polyvinyl pyrrolidone	5%
Stearyl alcohol	6%
Magnesium stearate	1%

(2) Preparation of tablets

The mixture obtained from the above (1) was compressed into a tablet by means of a rotary-type compressor so that the average hardness of tablet is 20 kg/cm^3 or more.

(3) Preparation of capsules

The mixture obtained from the above (1) was formulated into the granules by means of a dry granulator and the granules thus prepared were passed through a 16 mesh screen to establish the granules having a uniform size, which were then filled in No.1 type capsule.

Example 3

(1) Mixing

The following components were introduced into a mixer in the given % by weight and then mixed together:

Praziquantel	46.9%
Hydroxypropyl methylcellulose	46.9%
Polyvinyl pyrrolidone	3.4%
Stearic acid	1.9%
Magnesium stearate	0.9%

(2) Preparation of tablets

The mixture obtained from the above (1) was compressed into a tablet by means of a rotary-type compressor so that the average hardness of tablet is 20 kg/cm^3 or more.

(3) Preparation of capsules

The mixture obtained from the above (1) was mixed with a mixed solution of water for granulation (50%) and ethanol (50%) and then granulated, and the resulting granules were dried over a plate drier. The granules thus prepared were passed through a 16 mesh screen to establish the granules having a uniform size, which were then filled in No.1 type capsule.

Example 4

(1) Mixing

The following components were introduced into a mixer in the given % by weight and then mixed together:

Praziquantel	45.3%
Hydroxypropyl methylcellulose	40.3%
Polyvinyl pyrrolidone	5.4%
Stearic acid	8.1%
Magnesium stearate	0.9%

(2) Preparation of tablets

The mixture obtained from the above (1) was compressed into a tablet by means of a rotary-type compressor so that the average hardness of tablet is 20 kg/cm^3 or more.

(3) Preparation of capsules

The mixture obtained from the above (1) was formulated into the granules by means of a dry granulator and the granules thus prepared were passed through a 16 mesh screen to establish the granules having a uniform size, which were then filled in No.1 type capsule.

Experiment 1: Test for dissolution

The preparations produced from (2) and (3) of Example 1, (2) and (3) of Example 2, (2) and (3) of Example 3 and (2) and (3) of Example 4 were subjected to the test for dissolution according to the second method for evaluating dissolution as defined in U.S.P., using 900 ml of 0.1N HCl solution as the dissolving solution at temperature

of 37°C. The result thus obtained is described in the following Tables 1 through 8.

Table 1

Result of the test for dissolution of the tablet preparation prepared by (2) of Example 1

Hour	Released amount (%)
1.0	10.8
2.0	17.2
3.0	25.1
4.0	37.6
5.0	46.1
6.0	54.2
7.0	62.7
8.0	72.7
9.0	80.3
10.0	91.4

Table 2

Result of the test for dissolution of the capsule preparation prepared by (3) of Example 1

Hour	Released amount (%)

1.0	10.8
2.0	17.2
3.0	20.4
4.0	29.9
5.0	38.1
6.0	47.2
7.0	58.4
8.0	72.9
9.0	82.8
10.0	87.9

Table 3

Result of the test for dissolution of the tablet preparation prepared by (2) of Example 2

Hour	Released amount (%)
1.0	5.8
2.0	16.4
3.0	25.4
4.0	34.4
5.0	46.3
6.0	53.9
7.0	66.0

8.0	73.8
9.0	89.2
10.0	91.0

Table 4

Result of the test for dissolution of the capsule preparation prepared by (3) of Example 2

Hour	Released amount (%)
1.0	7.2
2.0	13.9
3.0	22.7
4.0	34.6
5.0	42.1
6.0	57.8
7.0	64.7
8.0	71.1
9.0	87.9
10.0	93.4

Table 5

Result of the test for dissolution of the tablet preparation prepared by (2) of Example 3

Hour	Released amount (%)
1.0	9.6
2.0	11.5
3.0	23.7
4.0	31.4
5.0	44.7
6.0	58.9
7.0	63.8
8.0	74.5
9.0	91.3
10.0	99.8

Table 6

Result of the test for dissolution of the capsule preparation prepared by (3) of Example 3

Hour	Released amount (%)
1.0	8.8
2.0	13.1
3.0	20.6
4.0	29.9

5.0	39.4
6.0	51.3
7.0	63.2
8.0	76.2
9.0	84.3
10.0	98.9

Table 7

Result of the test for dissolution of the tablet preparation prepared by (2) of Example 4

Hour	Released amount (%)
1.0	7.4
2.0	10.7
3.0	20.1
4.0	26.4
5.0	35.2
6.0	44.6
7.0	55.3
8.0	63.9
9.0	77.8
10.0	89.9

Table 8

Result of the test for dissolution of the capsule preparation prepared by (3) of Example 4

Hour	Released amount (%)
1.0	7.4
2.0	10.7
3.0	20.1
4.0	26.4
5.0	35.2
6.0	44.6
7.0	55.3
8.0	63.9
9.0	77.8
10.0	89.9

According to the result of above test, it could be identified that the preparations of the present invention are controlled so that praziquantel is slowly released from the preparation since all of the tablet and capsule preparations according to the present invention continuously release praziquantel as the active ingredient over 10 hours or more.

Experiment 2: Test for blood concentration of sustained-releasing praziquantel preparation in dogs

The blood concentration of praziquantel from the sustained-releasing tablet preparation as prepared by Examples 1 and 3 was measured in an animal model comprising dogs. The control group received a presently commercially available praziquantel tablet, Distocid® as the comparative drug.

As the dose administered to animals, the comparative drug was administered via oral route in a single dose of 30 mg/kg of body weight to 3 dogs of the control group and the test drug was administered via oral route in a single dose of 30 mg/kg, 50mg/kg and 100 mg/kg of body weight to 5, 13 and 5 dogs, respectively.

Blood was taken from the test and control groups 1, 2, 3, 4, 6, 12 and 24 hours after drug administration, and the blood concentration of praziquantel was analyzed. The result was recorded in terms of the plasma level of praziquantel (μg/ml) per hour (h) and represented as "average ± standard deviation" in the following Tables 9 through 12.

Table 9

Change in blood concentration of praziquantel in the control group (Distocid®)

Hour	Control Group
1	18.6 ± 12.0
2	17.0 ± 9.6
3	12.8 ± 1.8
4	7.0 ± 1.8
6	2.5 ± 1.4

12	0.5 ± 0.1
24	0.4 ± 0.2

Table 10

Change in blood concentration of praziquantel in the 30 mg/kg test group

Hour	Example 1	Example 3
1	6.0 ± 5.7	7.2 ± 7.2
2	5.4 ± 5.6	6.2 ± 5.2
3	5.1 ± 4.9	5.2 ± 5.4
4	3.9 ± 3.2	3.1 ± 2.2
6	1.9 ± 1.8	2.1 ± 2.4
12	0.9 ± 0.8	1.2 ± 7.0
24	0.1 ± 0.4	0.3 ± 0.2

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Table 11

Change in blood concentration of praziquantel in the 50 mg/kg test group

Hour	Example 1	Example 3
1	9.9 ± 9.7	11.22 ± 12.8
2	13.8 ± 11.9	15.9 ± 15.0
3	15.7 ± 14.0	16.0 ± 11.8

4	12.5 ± 10.1	14.7 ± 8.5
6	8.5 ± 6.7	9.0 ± 5.9
12	1.2 ± 0.9	2.2 ± 1.7
24	0.4 ± 0.3	0.8 ± 1.4

Table 12

Change in blood concentration of praziquantel in the 100 mg/kg test group

Hour	Example 1	Example 3
1	10.0 ± 8.2	11.4 ± 3.8
2	12.7 ± 6.7	15.3 ± 6.8
3	18.4 ± 10.4	25.8 ± 19.3
4	13.6 ± 8.7	17.6 ± 9.4
6	11.4 ± 7.5	19.5 ± 12.0
12	3.7 ± 2.9	5.7 ± 5.7
24	0.3 ± 0.9	0.9 ± 1.1

According to the result of the above experiment, it could be noted that when the sustained-releasing praziquantel preparation as prepared in Examples 1 and 3 are administered in a dose of 30 mg/kg, 50 mg/kg or 100 mg/kg of body weight, the effective blood concentration of 1 μg/ml is maintained for 12 hours or more.

Experiment 3: Test for anthelmintic effect of the sustained-releasing praziquantel tablet using dogs

The anthelmintic effect of praziquantel from the sustained-releasing tablet prepared in Examples 1 and 3 was determined using dogs. The control group received a presently commercially available praziquantel tablet Distocid®.

First, dogs to be used in the experiment were infected with 500 metacercarias of *Clonorchis sinensis* per individual subject and, after 5 to 6 weeks from infection, the sustained-releasing praziquantel tablets prepared in Examples 1 and 3 and the comparative drug (Distocid®) were respectively administered to animals via oral route.

As the dose administered to animals, in the control group the presently commercially available Distocid® was administered via oral route in a dose of 30 mg/kg of body weight three times at intervals of 5 hours to 3 dogs according to the recommended usage, and in the test group the sustained-releasing tablets as prepared in Examples 1 and 3 were administered via oral route in a single dose of 30 mg/kg, 50mg/kg and 100 mg/kg of body weight to 4, 10 and 4 dogs, respectively.

The anthelmintic effect was determined by measuring worm recovery rate, cure rate and worm reduction rate. The result is given in the following Tables 13 through 16.

Table 13

Anthelmintic effect of Distocid®

Criteria	Control group
Worm recovery rate	0
Cure rate	100

Worm reduction rate	100

Table 14

Anthelmintic effect of the 30 mg/kg test group

Criteria	Example 1	Example 3
Worm recovery rate	1.8	0
Cure rate	50	100
Worm reduction rate	93.9	100

Table 15

Anthelmintic effect of the 50 mg/kg test group

Criteria	Example 1	Example 3
Worm recovery rate	1.1	0
Cure rate	84	100
Worm reduction rate	96.3	100

Table 16

Anthelmintic effect of the 100 mg/kg test group

Criteria	Example 1	Example 3

Worm recovery rate	0.1	0
Cure rate	97	100
Worm reduction rate	99.7	100

According to the result of the above experiment, it could be noted that the sustained-releasing praziquantel preparation as prepared in Examples 1 and 3 exhibit a sufficient anthelmintic effect even by a single oral administration in a dose of 30 mg/kg, 50 mg/kg or 100 mg/kg.

As reviewed above, since the sustained-releasing preparation of the present invention is designed so that praziquantel can be slowly absorbed within intestine, it can exhibit anthelmintic effect at the same level as the prior art preparations, even by a single administration, thereby providing a convenience of drug administration, and allow to improve a therapeutic effect against various trematode and taenia infections in tissues. Further, the prior art preparation causes inconvenience due to three times dosing at intervals of 4 to 6 hours whereas the sustained-releasing preparation of the present invention can exhibit the desired anthelmintic effect even by a single dosing so that a convenience of taking the drug can be expected.

In addition, in view of a total dose of praziquantel in treating clonorchiasis the prior art preparations should be administered in an amount of 4.5 g over three times for adult man having 60 kg of body weight whereas it is expected that the sustained-releasing preparation of the present invention can exhibit a sufficient anthelmintic effect even by a single dose of 1.8 g.

Therefore, it can be expected that the sustained-releasing preparation according to the present invention solve the inconvenience of the prior art preparations due to

three times dosing per day, greatly reduce the side effects, which may be induced by overdosing of the drug, eliminates any possibility of occurring resistant worms due to infector's incompliance of a regular time for taking the drug, and further, allows to greatly reduce the cost incurred in treatment of various trematode and taenia infections in economical view.

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes can be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

CLAIMS

1. A sustained-releasing anthelmintic composition which comprises praziquantel; a polymeric material selected from the group consisting of hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, methylcellulose and ethylcellulose; a filler selected from the group consisting of alkyl alcohol, fatty acid and salt thereof; and a binder.

2. The composition of claim 1, wherein the polymeric material is contained in the ratio of 20 to 60 wt% with respect to a total weight of the composition.

3. The composition of claim 1, wherein the filler is stearic acid or stearyl alcohol.

4. The composition of claim 1, wherein the filler is contained in the ratio of up to 20 wt% with respect to a total weight of the composition.

5. The composition of claim 1, wherein the binder is polyvinyl pyrrolidone or hydroxypropyl cellulose having a low level of substitution.

6. The composition of claim 1, wherein the binder is contained in the ratio of 1.5 to 8.5 wt% with respect to a total weight of the composition.

7. The composition of claim 1, in the form of a pharmaceutical preparation of tablet or capsule.

8. The composition of claim 1, wherein the hardness of tablet preparation is 20 kg/cm^3 or more.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR00/01535

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 9/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)

IPC 7 : A61K

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Maggi et al. 'Formulation of biphasic release tablets containing slightly soluble drugs' In Eur. J. Pharm. Biopharm. 1999 July, Volume 48(1), page 37-42, see the entire document.	1-8
Y	US 4248858 A (American Home Products Corp.) 03 February 1981 (03. 02. 1981), see the entire document.	1-8

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
12 APRIL 2001 (12.04.2001)	16 APRIL 2001 (16.04.2001)

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Telephone No. 82-42-481-5609

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR00/01535

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